REMARKS

I. General

Applicants respectfully request reconsideration of the present application.

II. Disposition of the Claims

Claims 1-3, 5-24, and 28-50 were previously cancelled, without prejudice or disclaimer.

Claims 4 and 25-27 were previously presented and examined.

III. Claim Rejections – 35 U.S.C. § 102

Claims 4 and 25-27 are rejected under 35 U.S.C. § 102(a) as being anticipated by WO 98/11884. Office Action, pp. 2-3. In the Response filed August 20, 2007, this rejection was traversed, because a reference cannot anticipate what it fails to describe, and the need for picking and choosing from various compounds of Formula I and insulin sensitizers is required to reach an embodiment within the scope of the present claims, so that the invention is not squarely described. In the outstanding Office action, the Examiner disagreed and proceeded to pick and choose embodiments despite the controlling authority to the contrary. Office Action, pp. 2-3. This rejection is respectfully traversed.

The Examiner cited Verdegall Bros. v. Union Oil Co., 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) for the proposition that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Indeed, this black letter law statement shows why the Examiner's need for picking and choosing means there is no anticipation.

The presently claimed invention is a method for lowering the concentration of glycosylated hemoglobin in a mammal in need thereof, while WO 98/11884 relates to "a method of reducing insulin resistance in humans in who Impaired Glucose Tolerance (IGT) and Non-Insulin Dependent Diabetes Mellitus (NIDDM) have not presented."

The Examiner directed Applicants to the disclosure at pp. 12-13, concerning, e.g., a medicament for combination therapy of "NIDDM patients to improve their weight and diabetic control comprising a compound of formula I and an insulin sensitizing agent."

> The present invention further provides a method of improving the weight and diabetic control of NIDDM patients comprising the administration of a compound of formula I in combination with an oral insulin secretagogue or an insulin sensitising agent
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>
> in conjunction with a pharmaceutically acceptable diluent or carrier to a human in need thereof.

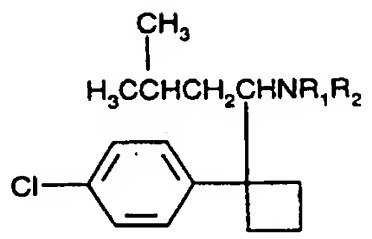
The element described as "an insulin sensitizing agent" is not necessarily *pioglitazone or its salt*. Many "insulin sensitizing agent[s]" exist {present specification, claim 2 as filed} and the "insulin sensitizing agent" is not necessarily *pioglitazone or its salt*. Thus, the disclosure of the term "insulin sensitizing agent" does not necessarily (inherently) mean that pioglitazone was described, nor does it encompass a genus small enough that each of its members would be anticipated if individually claimed.

The Examiner relied on various cases for the proposition that "WO884 explicitly [describes in a manner required under § 102] the use of the instantly claimed sibutramine as well as its combination with insulin sensitizing agents, preferably the claimed pioglitazone." Office Action, pp. 2-3 (Brown v. 3M, 265 F.3d 1349, 1351, 60 USPQ2d 1375, 1376 (Fed. Cir. 2001) ("When a claim covers several structures or compositions, either generically or as alternatives, the claim is deemed anticipated if any of the structures or compositions within the scope of the claim is known in the prior art. (Citations omitted)); Ex parte A, 17 USPQ2d 1716 (BPAI 1990) (see comments on page 3 Office action); and In re Sivaramakrishnan, 673 F.2d 1383, 213 USPQ 441 (CCPA 1982) (see comments on page 3 Office Action)). These cases, however, do not stand for the stated proposition. At best, these cases stand for the simple proposition that a compound or small group of combinations described in a prior art reference, and any generic claim including that compound or small group of combinations, are unpatentable under 35 U.S.C. § 102. Here, however, the claims do not embrace a

compound per se. They recite a particular method of use comprising *administering* not one, but two, different compounds. Thus, it is irrelevant to anticipation if the reference mentions two ingredients by name.

Even if *pioglitazone* is further highlighted as a preferable insulin sensitizing agent selected from metformin, ciglitazone, troglitazone, and *pioglitazone* (WO884, p. 13, ll. 6-7), referencing this list of "insulin sensitizing agent[s]" is picking and choosing, as implicitly recognized in the Examiner's statement "preferably the claimed pioglitazone." Office action, p. 3.

Similarly, in order to reach sibutramine from the genus of the "compound of formula I,"



including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl, in conjunction with a pharmaceutically acceptable

one of ordinary skill in the art would have to pick and choose one embodiment of the "compound of formula I." Selecting a member of the "compound of formula I" would not necessarily result in sibutramine.

As such, the disclosure from pages 12-13 of WO884 requires picking and choosing to select a particular "insulin sensitizing agent" and a particular "compound of formula I" before even having a chance of achieving an embodiment of the present invention. Thus, the anticipation rejection should be withdrawn.

Moreover, the Examiner does not disagree that, during prosecution of this Application's Parent Application No. 09/380,059, now U.S. Patent No. 6,329,403, there were claims reciting "a method for lowering the concentration of glycosylated hemoglobin," which claims Examiner R. Cook withdrew in an Office Action dated April 23, 2001 because they

were "directed to an invention that is independent or distinct from the invention originally claimed," i.e., a method of treating diabetes, diabetic complications, or IGT. April 23, 2001, Office Action, p. 2. The Examiner asserts that Examiner Cook's restriction was a "clear error." Office Action, p. 4.

But the correctness of restriction requirement of an issued patent cannot be revisited. In re Watkinson, 900 F.2d 230, 233, 14 U.S.P.Q.2d 1407, 1409 (Fed. Cir. 1990) (enclosed for consideration). In this family, the PTO has already held that the present subject matter is not the same as (35 U.S.C. § 102) or obvious (35 U.S.C. § 103) in view of treating diabetics, diabetic complications and IGT. Thus, the rejection should be withdrawn.

IV. Claim Rejections – 35 U.S.C. § 103

Claims 4 and 25-27 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Grossman et al. and Hauner in view of WO 93/03724. Office Action, pp. 7-9. More specifically, the Examiner argued that the Declaration did not demonstrate unexpected results by comparing the sum of high ends of concentration of HbA1c in the Group B (-0.6%) and Group C (-0.7%) to the high end of the Group D results (-1.6). This position is respectfully traversed.

A Supplemental Declaration under Rule 132 by Dr. Odaka (hereinafter the "Supplemental Declaration") accompanies this Response, addressing the Examiner's request of further clarification of the data presented in the Declaration of Dr. Odaka from 2003 (Office Action, p. 4). In the enclosed Supplemental Declaration, applicants further conducted a statistical analysis (in particular a Tukey Test) on the data of HbA1c concentration changes in the Declaration of Dr. Odaka 2003. It also includes corrections of minor clerical errors found upon review of the prior Declaration.

The Tukey Test is a statistical hypothesis test generally used for pairwise comparisons. If the calculated p-value is below the threshold chosen for statistic significance (0.05 for 95% confidence), the null hypothesis which states that the two groups do not differ

is rejected in favor of an alternative hypothesis, which typically states that the groups do differ.

As shown in the Supplemental Declaration, no significant difference was observed between Group B (using only pioglitazone) and Group A (control), Group C (using only sibutamine) and Group A (control), and also between Group B and Group C. However, the result of Group D differs from Groups A, B, and C significantly, showing an unexpected synergic effect of using the combination of pioglitazone and sibutramine.

The differences in results are in fact unexpected and unobvious and of both statistical and practical significance. Applicants, therefore, respectfully request the Examiner to withdraw the rejection. Ex parte Gelles, 22 USPQ2d 1318 (BPAI 1992).

CONCLUSION

It is believed that the present application is in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are

needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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By _____

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